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Metabolic Acid-Base Disorders

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KEYWORDS

• Metabolic • MUDPILES • Ketoacidosis • Acidosis • Alkalosis • Anion gap
• Chloride-sensitive

KEY POINTS

- A normal serum bicarbonate does not rule out a metabolic acidosis; a metabolic alkalosis may balance a high anion-gap metabolic acidosis. An anion gap should be calculated in every patient and adjusted for hypoalbuminemia (albumin is an anion that contributes to the anion gap); a delta-delta allows detection of mixed acid base disturbances.
- Additional testing in an anion gap metabolic acidosis includes plasma or urine ketones, lactic acid, salicylate, osmolal gap, and toxic alcohol testing. Once identified, treat the underlying cause of the metabolic acidosis.
- Metabolic alkalosis is most commonly due to excessive vomiting or diuretic use. It is often associated with hypokalemia; urine chloride may aid in diagnosing the underlying cause.
- Treat the underlying cause of alkalosis. In volume depletion, 0.9% normal saline and potassium chloride replete volume and chloride losses; in volume overload states, carbonic anhydrase inhibitors and potassium-sparing diuretics may be used.

INTRODUCTION

Acid-base disorders are commonly encountered in the acute care setting. Emergency clinicians must identify major acid-base disturbances and their underlying causes to prevent patient deterioration. The acid-base status is determined by laboratory studies. This status includes plasma pH, plasma bicarbonate (HCO_3^-), and the partial pressure of carbon dioxide (P_{CO_2}) from a blood gas.[1] Increases of bicarbonate or decreases of P_{CO_2} increase the pH of the blood, causing an alkalemia, whereas decreases of bicarbonate or increases in P_{CO_2} lower the pH of the blood, causing an

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acidemia. When the bicarbonate concentration of the blood is abnormal, it is called a metabolic acid-base disorder; changes in P_{CO_2} are called a respiratory acid-base disorder. Physiologically, P_{CO_2} levels are regulated through respiration, whereas bicarbonate levels are regulated through renal reabsorption rates.[2,3] The clinical history and other laboratory studies are necessary to determine the underlying cause of the acid-base disturbance.[2,4] The severity of clinical presentation and treatment depends on the underlying cause of the metabolic disorder.

A metabolic acidosis reduces the plasma bicarbonate and blood pH. It is generally defined as a plasma bicarbonate of less than 22 mmol/L and an acidemia with a pH lower than a normal value of 7.35.[2] A metabolic acidosis can be further divided into a high anion gap (HAGMA) and normal anion gap metabolic acidosis (NAGMA). A metabolic alkalosis, which is defined as an arterial pH greater than 7.45 and/or an increase in serum bicarbonate greater than 30 mmol/L, is commonly seen in patients without symptoms but can lead to respiratory and neurologic symptoms if the alkalosis becomes severe.[5,6] A mixed acid-base disorder, such as a metabolic acidosis and concomitant alkalosis, may result in a near-normal pH and plasma bicarbonate but still contain a significant acid-base disturbance for the patient.

A venous blood gas and arterial blood gas are both adequate in assessing the pH. The venous pH is on average 0.03 to 0.04 less than the arterial pH in ED patients.[7–9] In clinical practice, an arterial pH less than 7.35 is an acidemia and greater than 7.45 is an alkalemia. A normal serum bicarbonate is 24 ± 2 mmol/L. A normal anion gap ranges from 8 to 12 mmol/L (mEq/L). The exact reference values depend on the laboratory analyzer.

Additional diagnostic studies will be required to identify the underlying cause once a metabolic acid-base disorder has been identified. These include plasma ketones (beta-hydroxybutyrate), urinalysis (urine ketone nitroprusside test to detect acetoacetic acid), ethanol, lactate, albumin, serum osmolality, toxic alcohol panel, urine chloride concentration, renin and aldosterone levels.

METABOLIC ACIDOSIS

A low plasma bicarbonate (ie, < 22 L mmol/L (mEq/L)) defines a metabolic acidosis (**Fig. 1**). The arterial pH is generally less than 7.38 unless a secondary acid-base disturbance is present.[3]

Once the metabolic acidosis has been defined as high anion gap or normal anion gap, the differential diagnosis can be narrowed (**Table 1**).

Clinical Presentation

The presentations of patients with a metabolic acidosis range from mild illness to critically ill depending on the cause and severity. The first step in diagnosis is a thorough medical history and clinical examination. Patients often present with nonspecific complaints including abdominal pain, nausea, and vomiting, and, as the acidemia worsens, patients develop hemodynamic instability and mental status changes. Rapid deep breathing indicates a respiratory compensation for an acute metabolic acidosis. The history and physical examination are helpful, not for the recognition of a metabolic acidosis but for the investigation into a possible cause.

High anion gap metabolic acidosis evaluation and causes

In a normal physiologic state, the sum of cations is equal to and balances the sum of the anions. The primary cation is sodium; potassium can be omitted from the anion gap calculation because it is relatively low in concentration.[10] The primary anions are chloride and bicarbonate; the additional anions are the “anion gap” and include

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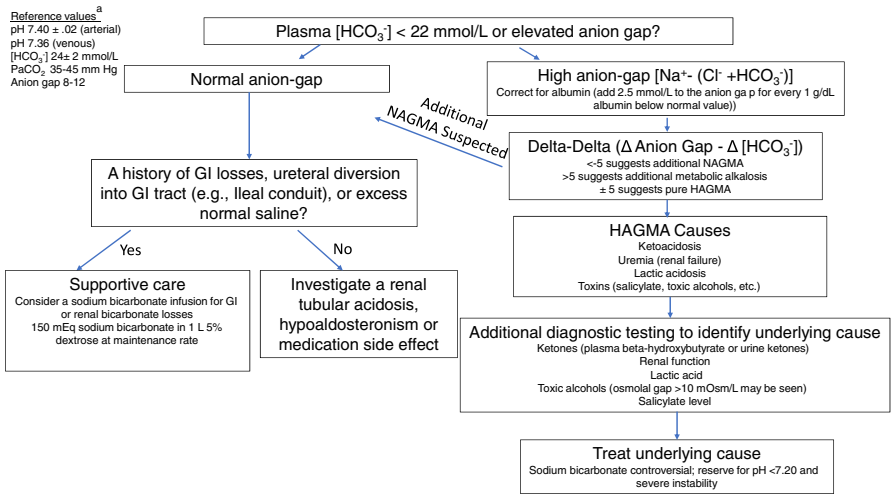
Reference values[a]
pH 7.40 ± .02 (arterial)
pH 7.36 (venous)
[HCO3-] 24± 2 mmol/L
PaCO2 35-45 mm Hg
Anion gap 8-12
Plasma [HCO3-] < 22 mmol/L or elevated anion gap?
Normal anion-gap
High anion-gap [Na+- (Cl- +HCO3-)]
Correct for albumin (add 2.5 mmol/L to the anion ga p for every 1 g/dL albumin below normal value))
Additional NAGMA Suspected
Delta-Delta (Δ Anion Gap - Δ [HCO3-])
<-5 suggests additional NAGMA
>5 suggests additional metabolic alkalosis
± 5 suggests pure HAGMA
A history of GI losses, ureteral diversion into GI tract (e.g., Ileal conduit), or excess normal saline?
HAGMA Causes
Ketoacidosis
Uremia (renal failure)
Lactic acidosis
Toxins (salicylate, toxic alcohols, etc.)
Yes
No
Supportive care
Consider a sodium bicarbonate infusion for GI or renal bicarbonate losses
150 mEq sodium bicarbonate in 1 L 5% dextrose at maintenance rate
Investigate a renal tubular acidosis, hypoaldosteronism or medication side effect
Additional diagnostic testing to identify underlying cause
Ketones (plasma beta-hydroxybutyrate or urine ketones)
Renal function
Lactic acid
Toxic alcohols (osmolal gap >10 mOsm/L may be seen)
Salicylate level
Treat underlying cause
Sodium bicarbonate controversial; reserve for pH <7.20 and severe instability

Fig. 1. The evaluation and management of metabolic acidosis. GI, gastrointestinal; HAGMA, high anion gap metabolic acidosis; NAGMA, normal anion gap metabolic acidosis. [a] reference ranges vary by laboratory analyzer.

protein (eg, albumin), sulfate, and phosphate. Albumin is the anion that contributes the most to the anion gap.[4,10] Hyperalbuminemia increases the normal anion gap; hypoalbuminemia reduces the normal anion gap; this can be corrected by increasing the calculated anion gap by 2.5 mmol/L for every 1 g/dL decrease of serum albumin

Table 1
Differential for a high anion gap and normal anion gap metabolic acidosis[2,4,12,13,15,17,24]

Differential for a high anion gap metabolic acidosis	
*K*etoacidosis	Diabetic ketoacidosis Alcoholic ketoacidosis Starvation ketoacidosis
*U*remia	Renal failure
*L*actate	Lactic acid (type A and type B)
*T*oxins	Salicylate toxicity Toxic alcohols (methanol, ethylene glycol, propylene glycol, isopropanol, diethylene glycol) Cyanide and carbon monoxide 5-Oxoproline (pyroglutamic) Toluene Iron and isoniazid toxicity
Other causes	Rhabdomyolysis
Differential for a normal anion-gap metabolic acidosis	
Medications	Normal saline (large volumes) Acetazolamide
GI losses	Diarrhea Cholestyramine Ureteral diversion into ileal conduit
Renal Tubular Acidosis	Suspect in the absence of GI symptoms or medication cause

Abbreviation: GI, gastrointestinal.

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from normal levels (ie, 4.5 g/dL).[4,11,12] The normal anion gap derived from healthy volunteers is about 12 mmol/L ± 2; the normal reference range is usually 8 to 12 mmol/L but varies slightly between each laboratory analyzer.[4,10,12] An anion gap greater than reference range, or patient's baseline, means there is an unaccounted-for anion that may be pathologic (see **Table 1**). An HAGMA is correctly detected by calculating an anion gap and correcting it for albumin levels:

$$\text{Anion Gap} = Na^{+} - (Cl^{-} + HCO_3^{-})$$

Corrected for albumin (add 2.5 mmol/L to the calculated anion gap for every 1 g/dL albumin decrease less than normal value)

There are many mnemonics for the differential of a high anion gap metabolic acidosis. These mnemonics commonly include MUDPILES, GOLD MARK, and KULT.[13]

- MUDPILES: *M*ethanol, *U*remia, *D*iabetic ketoacidosis, *P*araldehyde, *I*ron and Isoniazid, *L*actate, *E*thylene glycol, and *S*alicylate
- GOLD MARK: *G*lycols (ethylene and propylene), *O*xoproline, *L*-lactate, *D*-lactate, *M*ethanol, *A*spirin, *R*enal failure, and *K*etoacidosis.
- KULT: *K*etoacidosis, *U*remia, *L*actate, and *T*oxins is the simplest mnemonic (see **Table 1**).

If the cause of the anion gap is not readily apparent, laboratory testing of plasma lactate, ketones, and salicylates is recommended.[14] Other causes of an HAGMA include widespread cellular lysis such as rhabdomyolysis.[2] If this is suspected, check a plasma creatine kinase (CK).

Ketoacidosis. A ketoacidosis occurs when fatty acid metabolism leads to ketone production out of proportion to ketone metabolism. The ketones are buffered by bicarbonate, causing a drop in plasma bicarbonate and increase in the anion gap; this may occur during times of starvation, insulin deficiency (ie, diabetic ketoacidosis), or in metabolic disturbances caused by ethanol use. The 2 dominant forms of ketones are acetoacetic acid and beta-hydroxybutyrate; the balance of each is determined by the cause and the balance of nicotinamide adenine dinucleotide (NADH/NAD+). This is relevant to clinical practice because alcoholic ketoacidosis produces mostly beta-hydroxybutyrate, due to an elevation in nicotinamide adenine dinucleotide and hydrogen (NADH), which is not detected on urinalysis ketone nitroprusside testing.[15,16]

Diabetic ketoacidosis is the most common severe ketoacidosis in practice. It is usually defined by elevated ketones (blood or urine), HAGMA (anion gap > 10, serum bicarbonate $\leq$ 18 mEq/L), acidemia (pH < 7.30), plasma glucose greater than or equal to 250 mg/dL, and often a history of diabetes.[17] The differential of HAGMA with ketonemia also includes starvation ketoacidosis and alcoholic ketoacidosis. Examples of starvation ketoacidosis commonly seen in clinical practice include hyperemesis gravidarum and gastrointestinal (GI) illnesses with poor oral intake; the acidosis is typically mild with the serum bicarbonate is usually $\geq$ 18 mmol/L.[16] An alcoholic ketoacidosis is associated with ethanol use, vomiting, and poor nutritional intake. The underlying cause is from poor glycogen stores and an elevated NADH due to ethanol metabolism.[15,16] Alcohol ketoacidosis may also have an elevated lactate due to deranged metabolism but it is often less than 4 mmol/L; high elevation should prompt evaluation of other causes.[15]

Uremia (renal failure). The HAGMA seen in renal failure is from the failure of glomerular filtration to filter excess anions and failure of the nephron to excrete metabolically

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produced acids. In renal failure the anion gap is typically between 20 and 25 mmol/L; a higher elevation should prompt evaluation for another cause.[10] It is generally seen in advanced renal failure when the filtration rate is less than 20 mL/min. Renal function should be assessed in any patient with a metabolic acidosis.

Lactic acidosis. A lactic acidosis represents overproduction of lactic acid, failure to metabolize lactic acid, or a combination of both.[4,18] Generally, each mmol/L elevation of serum lactate in an acute lactic acidosis will cause an equal reduction in serum bicarbonate unless there is more than one process (eg, shock).[10] Importantly, a small but clinically relevant increase in lactate between 3.0 and 5.0 mmol/L may not cause an appreciable increase in anion gap beyond normal values.[2] A lactic acidosis can be seen from many causes. In the clinical setting, a lactic acidosis can be subdivided into a type A lactic acidosis (global or regional perfusion impairment) and type B lactic acidosis (no sign of tissue perfusion impairment).[4,14] There is often overlap of both types. Type A is caused by tissue hypoxia and is the form seen in various types of shock. There are many toxic illnesses and medications that impair normal aerobic metabolism, leading to a lactic acidosis (type B), which include toxic alcohols (methanol, ethylene glycol, propylene glycol), salicylates, cyanide poisoning, and carbon monoxide poisoning. Medications that may cause a lactic acidosis include stimulation of aerobic glycolysis by beta-agonists (eg, albuterol, epinephrine), propofol infusion syndrome, antiretroviral agents, and metformin.[18] Metformin, in the setting of overdose, renal or hepatic dysfunction, has been associated with a severe lactic acidosis through an interference with oxidative phosphorylation.[18] Thiamine deficiency impairs pyruvate dehydrogenase, leading to a lactic acidosis. A plasma lactic acid should be obtained if a lactic acidosis is suspected.

Toxins. The differential of a severe anion gap metabolic acidosis should include toxicities leading to the accumulation of organic acids. The expanded mnemonic of GOLD MARK may help recall the wide differential of toxins.

Toxic alcohols

Toxic alcohols (methanol, ethylene glycol, isopropanol, diethylene glycol, propylene glycol) cause intoxication and are metabolized into toxic metabolites.[19] Their metabolites may also form lactic acid or ketones (acetone). A lactic acidosis is commonly seen in methanol and ethylene glycol toxicity. Patients often present with a depressed mental status, abdominal pain in an acute ingestion, followed later by organ dysfunction.[19]

- Methanol poisoning is associated with visual changes and blindness in severe cases.
- Ethylene glycol (the active ingredient in antifreeze) is metabolized into many toxic products, leading to neurologic changes followed by cardiovascular collapse and renal failure from calcium oxalate crystal deposition.[19]
- Isopropanol intoxication (eg, rubbing alcohol, hand sanitizers) can cause respiratory failure and cardiovascular collapse.[19]
- Propylene glycol is found in some forms of antifreeze and as a diluent in parenteral medications (eg, lorazepam infusion) and may cause an elevated anion gap and lactic acidosis.[19]
- Diethylene glycol (brake and hydraulic fluids) may cause abdominal pain, vomiting, altered mental status, renal failure, and peripheral neuropathy.[19]

Direct testing of toxic alcohols should be obtained if the diagnosis is suspected. This testing may not be readily available, necessitating screening with an osmolal gap. An osmolal gap is often elevated in an acute ingestion of toxic alcohols.

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Osmolal gap:

[Serum osmolality = 2(serum Na^+ mmol/L [mEq/L]) + BUN (mg/dL)/2.8 + glucose(mg/dL)/18]—serum measured osmolality.

The osmolal gap is normally less than 10 mOsm/L.[2,19] The osmolal gap is elevated in acute intoxications from toxic alcohols. Once the alcohol is metabolized into organic acid the anion gap increases and osmolal gap decreases.[19] Ethanol should also be measured; the measured value (mg/dL) is divided by 3.7 and added to the calculated serum osmolality.[20] Unfortunately, an osmolar gap lacks specificity and can be elevated with a lactic acidosis, renal failure, alcoholic and diabetic ketoacidosis (acetone), and others.[2,16] Similarly, an osmolal gap can be normal in toxic alcohol ingestion, limiting its sensitivity.[19] However, an elevated osmolar gap greater than 10 mOsm/L, HAGMA, and/or a supportive history suggesting toxic alcohol ingestion warrants treatment.

Salicylate toxicity

Salicylate toxicity stimulates hyperventilation (respiratory alkalosis) and causes an HAGMA. Importantly, this combination may result in a normal or elevated pH.[4] Salicylate itself, along with stimulation of the production of organic acids, leads to an increased anion gap. If salicylate toxicity is suspected, a plasma salicylate level should be obtained.

Other toxic causes

Many other toxic substances can cause an HAGMA. These substances should be further evaluated depending on the clinical evaluation.

- 5-Oxoproline (pyroglutamic) acidosis may occur in chronic acetaminophen use (even at therapeutic levels) in those who are malnourished.[4]
- Cyanide and carbon monoxide interfere with mitochondrial oxidative phosphorylation, leading to cellular injury and a lactic acidosis.[21,22] Carbon monoxide poisoning is diagnosed by a suggestive history and elevated carboxyhemoglobin levels. Cyanide toxicity may only be identified by exposure or access to cyanide with unexplained unresponsiveness, cardiovascular instability, and lactic acidosis.[22]
- Toluene toxicity can be experienced by sniffing glue or spray paint inhalation. The toluene is rapidly metabolized into benzoic acid and then converted into hippuric acid. Hippurate leads to an HAGMA but is rapidly excreted by the kidney. This rapid excretion may lead to volume depletion and potassium loss, resulting in a hypokalemia and NAGMA by the time the patient presents for care.[4]
- Acute iron poisoning disrupts oxidative phosphorylation, resulting in shock, multiorgan failure, and HAGMA (lactic acidosis).[13]
- Isoniazid (a medication used in the treatment of tuberculosis) toxicity may cause refractory seizure and a severe HAGMA (lactic acidosis).[23]

Mixed acid-base disturbance

If the anion gap is elevated but the serum bicarbonate level is near normal, a mixed acid-base disturbance may be present. A normal serum bicarbonate does not rule out an HAGMA. A mixed disorder of a metabolic alkalosis and HAGMA could present with a normal bicarbonate. An example encountered in practice is a starvation ketoacidosis (high anion gap) balanced with vomiting (loss of acid).

If an HAGMA is detected, a delta-delta should be calculated to determine if it is a pure HAGMA or mixed metabolic acid-base disorder. The delta-delta demonstrates that a pure HAGMA should result in a near equal elevation in the anion gap by roughly

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the same decrease in the plasma bicarbonate from normal values ([HCO_3^-] of 24 mmol/L, anion gap of 12 mmol/L). If the bicarbonate is lower than expected this suggests an additional NAGMA; if the bicarbonate is higher than expected this suggests a concomitant metabolic alkalosis. In a pure ketoacidosis the change in bicarbonate and anion gap is near 1:1 within ± 5 mmol/L. In a lactic acidosis the decrease in bicarbonate is about 0.6 times the increase in anion gap within ± 5 mmol/L.[2]

Delta-delta equation: (Δ Anion Gap- Δ [HCO_3^-]) = 0 ± 5 mmol/L.

The normal $Paco_2$ (arterial) is 35 to 45 mm Hg. Respiratory compensation of metabolic acidosis triggers respiratory compensation by hyperventilation and a reduction in $Paco_2$.[4] The reduction in $Paco_2$ is predicted by Winters formula:

$$Paco_2 = (1.5 \times [HCO_3^-] + 8) \pm 2$$

or

$$Paco_2 = [HCO_3^-] + 15 \text{ mm Hg}$$

If the $Paco_2$ is not within the expected range, a second respiratory process is present. The maximal respiratory compensation is to a $Paco_2$ as low as 8 to 12 mm Hg.[4]

Normal anion gap metabolic acidosis

An NAGMA occurs when hydrochloric acid is accumulated or when bicarbonate is lost and replaced with a chloride anion, leaving the anion gap unchanged.[4] For this reason, an NAGMA is sometimes referred to as a hyperchloremic metabolic acidosis. It is most often the result of GI losses of bicarbonate from diarrhea or a renal tubular acidosis.[12] Excessive 0.9% normal saline therapy may also lead to an NAGMA through a chloride load balanced by renal losses in bicarbonate.[12]

Gastrointestinal losses. A surgical history or a history of diarrhea should be obtained from any patient with an NAGMA. A large volume of diarrhea will result in a loss of bicarbonate. Ureteral diversion into an ileal conduit allows the GI mucosa of the ileum to retain chloride from the urine and lose bicarbonate.[12] Cholestyramine may also lead to an NAGMA by GI losses of bicarbonate.

Renal causes. Early renal failure may cause an NAGMA by decreased acid excretion. Eventually an HAGMA also develops as the renal failure becomes more severe. A renal tubular acidosis (RTA) is another common renal cause of an NAGMA. An RTA causes a reduced reabsorption of bicarbonate in the renal tubules.[12] An RTA may be inherited, acquired, or related to medications. Acetazolamide, a carbonic anhydrase inhibitor, leads to urinary wasting of bicarbonate in the proximal renal tubule (RTA type 2) and a NAGMA.[12] The emergency clinician should recognize the pattern of hypoaldosteronism (type 4 RTA), which can be seen in primary adrenal insufficiency (among other causes), demonstrating hyperkalemia and an NAGMA.[12] In summary, an RTA should be considered when there is a hyperchloremic NAGMA with no GI losses, renal failure, or medications to explain the disturbance.

Management of Metabolic Acidosis

The mainstay of management of an HAGMA and an NAGMA is identifying and treating the underlying cause and providing supportive care. If volume repletion in a patient with a metabolic acidosis is required, balanced crystalloids (eg, lactated Ringer solution, Plasma-Lyte) rather than 0.9% sodium chloride is recommended. The balanced crystalloids do not contain excess chloride. The lactate and acetate buffers generate

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bicarbonate and have a mild alkalinizing effect; however, the benefit of balanced crystalloids in clinical practice over normal saline remains unclear.[25,26] In life-threatening cases of metabolic acidosis, hyperventilation to induce a respiratory alkalosis can be trialed as a temporizing method in those on mechanical ventilation.[14]

The treatment of an HAGMA should be directed at the underlying cause (**Table 2**). In the case of shock and renal insufficiency, renal replacement therapy should be considered in those with a pH less than 7.15.[14] The treatment of an HAGMA with sodium bicarbonate is controversial. Still, experts may recommend sodium bicarbonate supplementation if the pH is less than 7.20 in the setting of hemodynamic instability.[18,27] If used, a starting dose of 1 to 2 mmol/kg is recommended.[27] The goal is stabilization while addressing the underlying cause. The benefit of this strategy is not proved and risks hypocalcemia, rebound alkalosis when the HAGMA has resolved, and intracellular acidification by the rapid crossing of carbon dioxide into the cells.[18,27,28] Rapid boluses of sodium bicarbonate may enhance these risks.

A multicenter, open-label, randomized controlled, phase 3 trial of critically ill patients with a severe metabolic acidosis (pH < 7.20) compared sodium bicarbonate administration with placebo.[28] Those who received a 4.2% sodium bicarbonate infusion to target a pH greater than 7.30 showed no difference overall in 28-day mortality or organ failure at 7 days but did have a reduced need for renal replacement therapy. In the subgroup of those with acute renal failure, sodium bicarbonate was associated with an improvement in outcomes.[28] This study suggests sodium bicarbonate may be associated with benefit in a critically ill population with acute renal failure and severe metabolic acidemia. If sodium bicarbonate is given, an infusion or slow administration is recommended.

Table 2
Treatment of a metabolic acidosis depending on the cause

Treatment of High Anion-Gap Metabolic Acidosis	
Ketoacidosis	Diabetic ketoacidosis: insulin, volume and electrolyte repletion Alcoholic ketoacidosis: volume repletion, dextrose containing fluids or oral nutrition, thiamine supplementation Starvation ketoacidosis: nutritional support with oral carbohydrate or intravenous dextrose
Uremia (renal failure)	Treat underlying cause; renal replacement therapy may be required if severe acidemia or electrolyte abnormalities
Lactic acidosis	Resuscitation and restoration of organ perfusion if related to tissue hypoxia (i.e., shock) Treat underlying cause if not tissue hypoxia; renal replacement therapy may be required in severe cases of lactic acidosis (e.g.., metformin associated)
Toxins	Depends on underlying cause; often care is supportive and includes specific antidotes and renal replacement therapy in severe cases
Treatment of Normal Anion-Gap Metabolic Acidosis	
GI Losses	Volume repletion, isotonic sodium bicarbonate (e.g., 150 mEq of sodium bicarbonate in 1 liter of 5% dextrose) more rapidly improves bicarbonate losses
Medications	If severe, stop offending medication; normal saline (0.9% sodium chloride) may worsen a hyperchloremic metabolic acidosis
Renal tubular acidosis	Treatment depends on underlying cause; nephrology consultation recommended if severe

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In an NAGMA where bicarbonate is lost from GI or renal causes, an infusion of isotonic sodium bicarbonate (eg, 150 mEq of sodium bicarbonate in 1 L of 5% dextrose) will more rapidly replenish bicarbonate losses and correct the acidosis.[27,28] A strategy of intravenous bicarbonate administration while assessing the plasma bicarbonate, electrolytes, and pH every few hours should be considered. In an RTA, the treatment will depend on the underlying cause; expert consultation with a nephrologist should be considered.

METABOLIC ALKALOSIS

A metabolic alkalosis, typically seen in conjunction with hypokalemia, is a common metabolic acid-base disorder. A metabolic alkalosis is present when the arterial pH is greater than 7.45 and there is an elevated serum bicarbonate of greater than 30 mmol/L. It can become life-threatening by causing respiratory or neurologic deterioration as the pH increases to and sustains greater than 7.55.[29] The most rapid compensation for a metabolic alkalosis is hypoventilation to elevate the P_{CO_2}. If severe, hypoventilation may lead to hypoxemia.

A metabolic alkalosis is generated by excessive losses of hydrogen ions from the GI tract, alkali administration, excessive renal hydrogen ion losses, and/or by intracellular shift of hydrogen ions. GI and renal hydrogen losses commonly lead to hypokalemia and hypochloremia. Metabolic alkalosis persists only in the presence of impaired renal regulation of bicarbonate.[29,30] Common causes of impaired renal regulation include hypovolemia, chloride depletion, hypokalemia, reduced glomerular filtration rate, or hyperaldosteronism.[31,32]

The cause of a metabolic alkalosis is often diagnosed by obtaining a thorough clinical history. Treatment is generally aimed at supportive care, and electrolyte repletion; however, abnormalities in blood pressure and volume status need to be addressed more directly.[31] Once a specific cause is identified, it should be addressed to prevent persistence or progression of the alkalosis.

Clinical Presentation

The most common and clinically relevant causes of metabolic alkalosis are excessive vomiting and diuretic therapy (loop and thiazide diuretics). The cause of a metabolic alkalosis is often apparent from the history. A patient with metabolic alkalosis may be asymptomatic or complain of symptoms related to volume depletion or accompanying electrolyte abnormalities. Volume depletion may result in fatigue, muscle cramps, and postural lightheadedness, whereas hypokalemia, hypocalcemia, and hypomagnesemia (seen in chronic diuretic use or in the inherited renal tubulopathies [ie, Bartter and Gitelman syndromes]) may result in muscle weakness/spasms, tetany, paresthesia, cardiac arrhythmias, polyuria, and polydipsia. Mineralocorticoid excess syndromes typically lead to volume expansion and hypertension.[30] Severe, uncorrected metabolic alkalosis may result in agitation, disorientation, seizures, and even coma, particularly in patients with chronic liver disease.[5] The systemic alkaline pH will favor the conversion of ammonium (NH_4^+) into the unionized, neutral nitrogen compound ammonia (NH_3), potentially leading to clinical manifestations of hepatic encephalopathy.[33]

Causes of metabolic alkalosis

The main causes of metabolic alkalosis (**Table 3**) can be divided into 4 main groups: chloride depletion syndromes (often from GI and renal losses of hydrogen ions); mineralocorticoid excess syndromes; apparent mineralocorticoid excess syndromes; and excess alkali administration.[5,34]

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Table 3
Common causes of metabolic alkalosis[5,29]

Volume Loss Chloride-responsive Urine Chloride < 20 mEq/L	Volume Normal or Overloaded Chloride-unresponsive Urine Chloride > 20 meq/L
Vomiting Excessive nasogastric suctioning	Primary hyperaldosteronism
Villous adenoma High-volume ileostomy losses Chronic diarrhea Congenital chloridorrhea Laxative overuse	Renal artery stenosis Accelerated hypertension Renin-secreting tumor
Diuretic losses Gitelman syndrome Bartter syndrome Cystic fibrosis with excess sweating	Liddle syndrome Fludrocortisone administration
Other Causes	
Milk-alkali syndrome Excess bicarbonate administration Severe potassium deficiency	

Gastrointestinal. Large volume vomiting or nasogastric suctioning leads to excess hydrogen ion losses and are the most common causes of GI-related metabolic alkalosis; this may be seen in acute infectious illness or gastric outlet obstruction. Diarrhea typically causes an NAGMA; however, certain conditions associated with diarrhea may lead to metabolic alkalosis such as laxative overuse, villous adenoma, high-output ileostomy drainage, or congenital chloridorrhea.[34] The metabolic alkalosis is maintained because of hypovolemia, and the urine chloride is expected to be low (<20 mEq/L).

Renal. Renal hydrogen losses are commonly associated with loop or thiazide diuretics. The activation of the renin-aldosterone system by diuretics in combination with salt-wasting leads to loss of hydrogen ion secretion and a metabolic alkalosis.[29] Other less commonly seen causes include primary mineralocorticoid excess (primary hyperaldosteronism, Cushing syndrome, exogenous mineralocorticoids) and mineralocorticoid excess–like states such as Liddle syndrome, excess licorice ingestion (reduces cortisol degradation), and Bartter or Gitelman disease (defect in the renal tubules).[29] Mineralocorticoid excess typically leads to volume expansion, hypertension, hypokalemia, and an elevated urine chloride (>20 mEq/L). These causes may be diagnosed by a clinical history and laboratory studies for mineralocorticoid excess (eg, renin, aldosterone, cortisol). The compensation of a chronic respiratory acidosis will lead to renal compensation by a retention of bicarbonate, and this can be diagnosed using a clinical history and blood gas.

Excessive alkali or calcium administration. Exogenous sodium bicarbonate may cause a metabolic alkalosis. Sodium bicarbonate administration to patients with a metabolic acidosis can result in a rebound or postcorrection metabolic alkalosis.[27] In clinical practice this can occur if sodium bicarbonate is given to an HAGMA; once the process causing the anion gap resolves the residual bicarbonate may cause an alkalosis. If sodium bicarbonate therapy is used, monitoring of the pH, electrolytes, and plasma bicarbonate is recommended to prevent this complication. Milk-alkali

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syndrome is seen in excess calcium-containing antacid consumption (eg, calcium carbonate), leading to hypercalcemia, renal failure, and a metabolic alkalosis.[29]

Contraction alkalosis. Contraction alkalosis is a phenomenon that occurs when a large volume of sodium-rich, bicarbonate-low fluid is lost from the body; this occurs with diuretic use, cystic fibrosis (electrolyte loss by sweating), and congenital chloride diarrhea, among others. The net concentration of bicarbonate increases as a result, and the kidney cannot compensate because of hypovolemia.[30]

If the cause of metabolic alkalosis is unclear from the history and physical examination, assessment of urine chloride levels can be helpful. The urine chloride is also helpful in determining if the process is chloride responsive. An approach to the evaluation and management of metabolic alkalosis is outlined in **Fig. 2**.

Management of Metabolic Alkalosis

The primary goals of treating a metabolic alkalosis are to identify and correct the cause of excess bicarbonate generation and to reverse factors that are impairing renal excretion of excess bicarbonate. Clinical management of metabolic alkalosis is best guided by a patient's fluid status and their plasma electrolyte (eg, chloride, potassium) and blood gas measurements. If the serum bicarbonate level is elevated as a compensatory response to a primary respiratory acidosis, treat the underlying respiratory process.

The most common causes of metabolic alkalosis—vomiting and diuretic use—are easily identified by history. Volume depletion leading to metabolic alkalosis is typically associated with a low urine chloride ion concentration (<20 mEq/L).[30] If this is the case, a trial of chloride-containing fluid such as normal saline (0.9% sodium chloride) and correction of hypokalemia with potassium chloride is recommended.[2] If the urine chloride ion concentration is high, mineralocorticoid excess is on the differential. Confirm the diagnoses by measuring plasma renin, aldosterone, and cortisol levels or refer for outpatient testing.[5,29] If mineralocorticoid excess is identified or suspected, an endocrine specialist can help guide specific treatment and diagnostic evaluation.

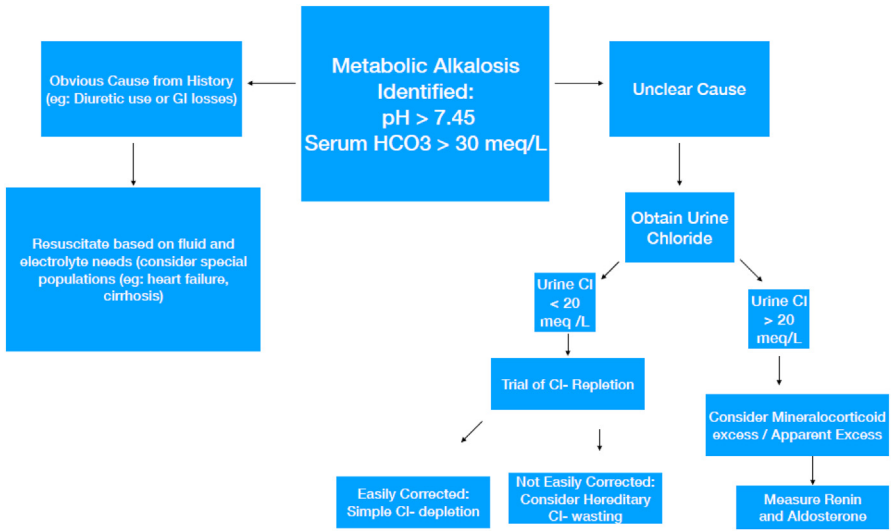
Metabolic Alkalosis Identified:
pH > 7.45
Serum HCO3 > 30 meq/L
Obvious Cause from History (eg: Diuretic use or GI losses)
Resuscitate based on fluid and electrolyte needs (consider special populations (eg: heart failure, cirrhosis)
Unclear Cause
Obtain Urine Chloride
Urine Cl < 20 meq /L
Urine Cl > 20 meq/L
Trial of Cl- Repletion
Consider Mineralocorticoid excess / Apparent Excess
Easily Corrected: Simple Cl- depletion
Not Easily Corrected: Consider Hereditary Cl- wasting
Measure Renin and Aldosterone

Fig. 2. Evaluation and management of metabolic alkalosis.

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Metabolic alkalosis is a common acid-base disorder in patients with congestive heart failure, commonly due to chronic diuretic use. In patients who develop a metabolic alkalosis while in a volume overload state (eg, congestive heart failure, cirrhosis) their reduced effective arterial blood volume is not truly related to a volume depleted state. Initial treatment of the metabolic alkalosis should be aimed at chloride and potassium repletion.[35,36] Hypokalemia plays an important role in the development and the persistence of metabolic alkalosis and should be replaced with intravenous or oral potassium chloride.[5] If further diuresis is required, carbonic anhydrase inhibitors, such as acetazolamide, can be used to increase urinary bicarbonate excretion and subsequently lower serum bicarbonate levels to target a normal pH.[36] Furthermore, aldosterone antagonists, also known as potassium-sparing diuretics such as spironolactone, may be helpful in these specific patients.[30,35] Critically ill patients with a metabolic alkalosis and acute or chronic kidney disease, who are not responding to or are not candidates for volume expansion, chloride repletion, potassium repletion, or administration of acetazolamide, will require treatment with low bicarbonate dialysis.[5,37]

Rarely, infusion of hydrochloric acid or a precursor such as ammonium chloride may be indicated to rapidly lower pH in patients with severe metabolic alkalosis (pH > 7.55 and/or serum bicarbonate level > 50 mEq/L) who cannot tolerate intravenous saline or potassium chloride administration because of volume overload or renal failure. This infusion should be performed in an intensive care unit with a nephrology or critical care consultation. These treatments must be administered through a central line due to high risk of sloughing of perivascular tissue.[5,38]

SUMMARY

Metabolic acid-base disorders are frequently encountered in the acute care setting. The key to evaluation and management of a metabolic acidosis includes a thorough clinical evaluation and narrowing the differential through the calculation of an anion gap. The underlying cause of a metabolic alkalosis is often clear from the history. If a metabolic alkalosis persists, and the conditions leading to it are not corrected, patients may develop neurologic and respiratory compromise. Supportive care and treatment targeting the underlying cause is the mainstay of management of metabolic acid-base disorders.

CLINICS CARE POINTS

- A normal serum bicarbonate does not rule out a metabolic acidosis; a metabolic alkalosis may balance a high anion gap metabolic acidosis. An anion gap should be calculated in every patient and adjusted for hypoalbuminemia (albumin is an anion that contributes to the anion gap); a delta-delta allows detection of mixed acid-base disturbances.
- Additional testing in an anion gap metabolic acidosis includes plasma or urine ketones, lactic acid, salicylate, osmolal gap, and toxic alcohol testing. Once identified, treat the underlying cause of the metabolic acidosis.
- Metabolic alkalosis is most commonly due to excessive vomiting or diuretic use (thiazides or loop diuretics). It is often associated with hypokalemia; urine chloride may aid in diagnosing the underlying cause.
- Treat the underlying cause of alkalosis. In volume depletion normal saline (0.9% chloride) and potassium chloride replete volume and chloride losses; in volume overload states carbonic anhydrase inhibitors and potassium sparing diuretics may be used.

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DISCLOSURE

The authors have no financial disclosures.

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